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Review

IL-17 signaling is regulated through intrinsic stability control of mRNA during inflammation

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Abstract: Interleukin (IL)-17 is a proinflammatory cytokine mainly produced by immune cells, especially activated T-helper 17 cells, which contribute to chronic inflammatory and autoimmune diseases including psoriasis. Although the molecular mechanisms of transcription in IL-17-mediated signaling pathways are well established, post-transcriptional control remains to be elucidated. Notably, IL-17 regulates post-transcriptional modifications, which induce elevated levels of target inflammatory mRNAs. Regnase-1, an endoribonuclease and deubiquitinase, post-transcriptionally downregulates various IL-17-driven signaling pathways, including mRNA stability. The ACT1-TBK1/IKKε pathway and ARID5A were induced and activated by IL-17-stimulation, leading to the inhibition of inflammatory mRNA degradation by Regnase-1. In this review, we focus on IL-17-mediated mRNA stabilization of psoriasis-related IκB-ζ and provide novel therapeutic strategies for the treatment of Th17-mediated inflammation and autoimmunity.

Keywords: IL-17; Th17; IκB-ζ; Regnase-1; mRNA stabilization; inflammation

1. Introduction

In 1986, Mosmann and Coffman introduced the concept of distinct types of T helper (Th) cells, which was based on the distinct cytokines profiles that T cells produce when they are stimulated to differentiate [1]. They described two types Th cells, type 1 helper T (Th1) cells and type 2 helper (Th2) T cells. Th1 cells, whose differentiation is promoted in the presence of IL-12, produce large amounts of interferon (IFN)-γ and are responsible for the host defense against intracellular pathogens. Th2 cells, whose differentiation is promoted in the presence of IL-4, produce IL-4, IL-5, and IL-13, and are responsible for host defense against extracellular pathogens. A novel Th17 subset has recently been identified [2,3]. In Th17 cells, transforming growth factor (TGF)-β, along with IL-6, triggers Th17 differentiation to produce IL-17 family cytokines, which promote neutrophil recruitment and antimicrobial peptide production, as well as reinforcing barrier function. IL-1β and IL-23 also activate Th17 cells, type 3 innate lymphoid cells (ILC3s), and γδ T-cell receptor bearing T cells (γδ T) to produce IL-17 [4] (Figure 1A). There are six IL-17 members: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F, of which IL-17A has been the most intensively studied [2,3]. All the family members except IL-17D are functional as homodimers, but IL-17A and IL-17F also form a heterodimer. There are five corresponding receptors: IL-17RA, IL-17RB/IL-25R, IL-17RC, IL-17RD/SEF, and IL-17RE. IL-17D was recently reported to bind CD93 [3] (Figure 1B). Notably, IL-17 and IL-17 producing cells are being revisited as inflammatory and/or autoimmune disease drivers [4]. In general, cytokine-driven inflammation is regulated by regulatory T (Treg) cells as well as anti-inflammatory cytokines such as IL-10, TGF-β, and IL-35 [5]. However, dysregulated IL-17 responses have been implicated in the pathogenesis of autoimmune diseases as well as various inflammation-based diseases, such as cardiovascular and neurological diseases [6,7]. Consequently, the IL-17 signaling pathway is believed to be a key target for the development of therapeutic drugs for autoimmune and chronic inflammatory diseases [4]. Regarding to IL-17-promoted elevation of inflammatory mRNAs, in addition to transcriptional events, IL-17 signaling protects inflammatory mRNAs from degradation through the inhibition of Regnase-1, an endoribonuclease [8,9]. Regnase-1 functions are controlled by several proteins to recognize specific sequences and/or RNA structure after IL-17-stimulation [8,9]. Here, we describe the current knowledge of the impact of IL-17-mediated signaling and its novel role in the intrinsic stability control of mRNA during inflammation.

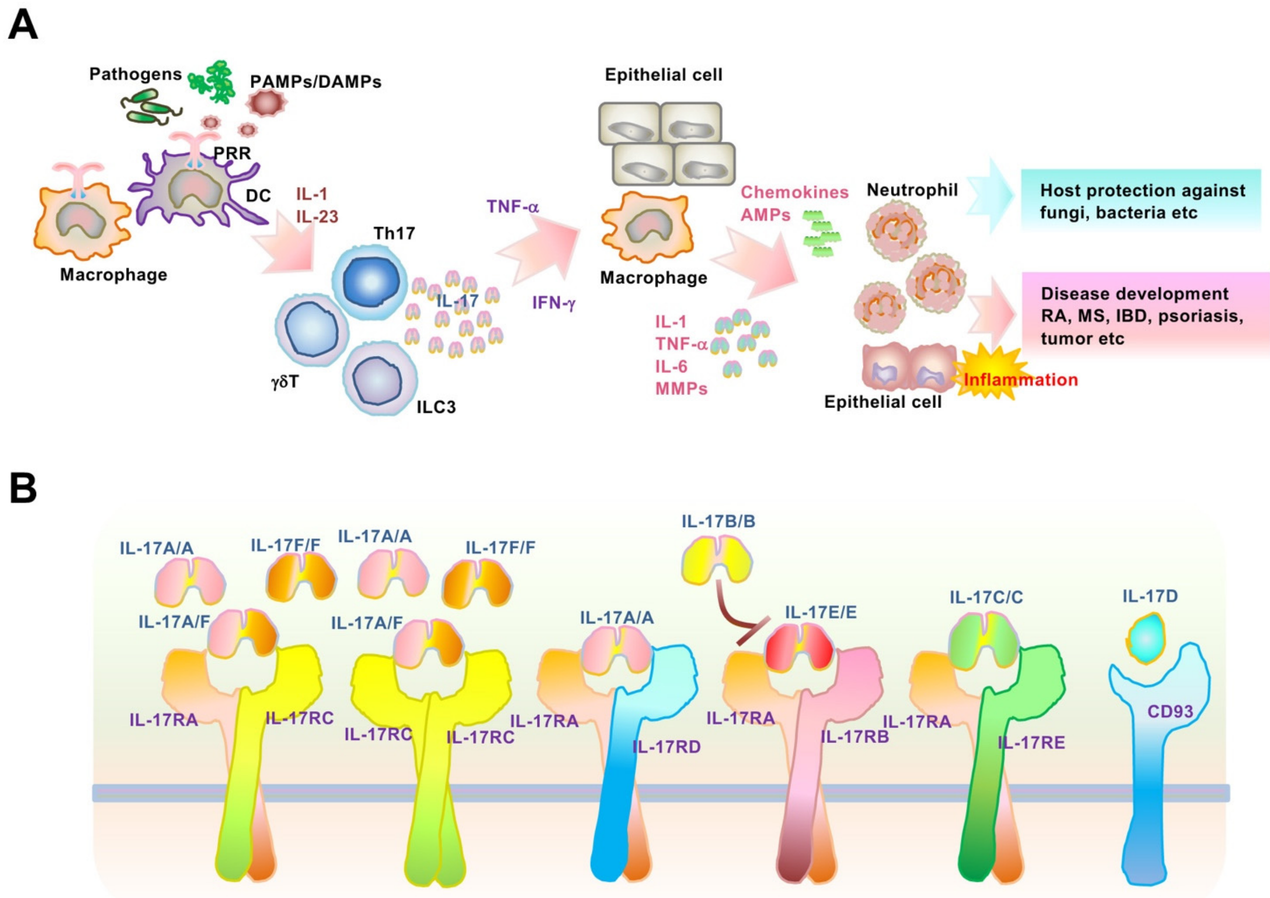

Figure 1. Role of IL-17 in immunity and immunopathology. A, Binding of PAMPs and DAMPs to PRRs promotes a set of immune responses against infection. Activated macrophages and DCs present foreign peptide antigens to T cells, as well as provide a source of T cell-polarizing cytokines. IL-1β and IL-23 activate Th17 cells, ILC3s, and γδT cells to produce IL-17, which promotes neutrophil-recruiting chemokine production from epithelial cells. IL-17, together with IFN-γ, activates macrophages to phagocytose and kill intracellular bacteria, fungi and protozoan parasites. IL-17, together with TNF-α, induce AMPs production and strengthen epithelial barrier function. These immune responses against infections sometimes generate auto-antigen-specific Th17 cells, which act on epithelial cells to produce chemokines that recruit neutrophils and macrophages. IL-17 also activates the production of pro-inflammatory cytokines and MMPs that induce tissue damage, leading to autoimmune diseases [4]. B, IL-17 receptor family ligand–receptor relationships are also shown. Six IL-17 family cytokines (IL-17A–IL-17F) and five members of the IL-17 receptor family (IL-17RA–IL-17RE) have been identified. PAMPs: pathogens release pathogen-associated molecular patterns; DAMPs: damage-associated molecular patterns; ILC3s: type 3 innate lymphoid cells; γδT: γδ T-cell receptor-bearing T cells; AMPs: antimicrobial peptides; MMPs: matrix metalloproteinases; RA: rheumatoid arthritis; MS: multiple sclerosis; IBD: inflammatory bowel disease.

2. IL-17-mediated signaling

IL-17 recognizes IL-17RA and IL-17RC receptor subunits, both of which have a conserved signaling motif, SEFIR (SEF/IL17R). This leads to the engagement of ACT1, an adaptor/ubiquitin ligase enzyme, which in turn recruits tumor necrosis factor receptor–associated factor (TRAF) 6 to activate the nuclear factor-κB (NF-κB) pathway [3,10]. ACT1 also lies upstream of the CCAAT/enhancer binding protein (C/EBP)-β and C/EBP-δ as well as the mitogen-activated protein kinase (MAPK) pathways, all of which regulate target gene expression. Both NF-κB and C/EBP are essential for IL-17-promoted transcriptional activities. Notably, IL-17 synergizes with IL-1β, IL-22, IFN-γ, TNF-α, and others to regulate its downstream gene expression [11]. However, the detailed molecular mechanisms underlying this synergistic signaling have not been fully elucidated. For example, IL-17-stimuli weakly induces the expression of chemokine (C-X-C motif) ligand (CXCL) 1, CXCL2, IL-6, IκB-ζ, and CXCL5 mRNAs, which are degraded rapidly. However, mRNA stability was significantly elevated in the presence of both IL-17 and TNF-α. The MAPK pathway and ACT1, but not TRAF6, were involved in this synergistic effect. In addition, joint stimulation with IL-17 and TNF-α co-operatively induced transcriptional activity of the IL-6 promoter by C/EBP, but not NF-κB. IL-17 also positively regulates TNF receptor expression, leading to enhanced TNF-α signaling in the presence of IL-17 [11]. Similarly, the synergistic effects of IL-17 and IL-19/IL-20/IL-24 are dependent on IL-22 receptor expression [12]. Therefore, although IL-17 is generally a weak inducer of target genes, this cytokine has a major impact *in vivo*; IL-17 synergistically acts with various cytokines to dictate its physiological activities.

3. Regulation of inflammatory mRNA stability by RNA binding proteins (RBPs)

To eliminate invading microorganisms or repair tissue injury, the sequential order of inflammatory events occurs under the control of preset gene activation programs. This process is probably a result of the interplay among elements that control transcriptional induction or repression, as well as mRNA stability [13,14].

mRNAs encoding inflammatory mediators (inflammatory mRNAs) are relatively unstable, enabling the fine-tuning of gene expression during inflammatory responses (Figure 2) [8,9,14]. The rapid turnover of such unstable mRNAs comes from various sequence/structural characteristics in their 3′ untranslated region (UTR), termed cis elements, in which a set of RBPs positively or negatively regulates mRNA stability. Among canonical cis-elements, the best-characterized motifs are the AU-rich element (ARE) and stem-loop structures, both of which are often found in the 3’-UTR of inflammatory mRNAs. AREs typically contain a stretch of adenine and/or uridine sequences, such as a repetitive AUUUA sequence. There are several ARE-binding proteins, such as tristetraprolin (TTP), Zinc-finger protein (ZFP) 36L1, ZFP36L2, AU-rich binding factor 1, human antigen R (HuR), and KH-type splicing regulatory proteins; most of these proteins promote target mRNA degradation. The stem-loop structure forms a hairpin-like shape, which is found on the mRNAs of *IL6*, *TNF*, *IL2*, inducible T-cell costimulator (*ICOS*), IκB-ζ (*NFKBIZ*), and IκB-δ (*NFKBID*). Stem-loop structures occasionally carry constitutive decay elements, which are targeted by Roquin-1 and Roquin-2. ARE and stem-loop structures exist in partially overlapping sets of

inflammatory mRNAs. mRNAs carrying these characteristic stem-loops are degraded by a set of RBPs, Regnase-1 (Zc3h12a), and Roquin-1 and -2 [8,9]. These RBPs are counteracted by another RBP, AT-rich interactive domain-containing protein 5A (ARID5A) [15]. Members of the Regnase family have PIN-like ribonuclease domains, as well as CCCH-type zinc-finger domains. Regnase-1 recognizes the particular stem-loop structures in the 3' UTR of inflammatory mRNAs (such as *Il6*, *Ptgs2*, and *Regnase-1*), and post-transcriptionally degrades them via endonucleolytic activity. Thus, Regnase-1 plays an essential role in the negative regulation of inflammatory mRNAs expression. Indeed, Regnase-1-deficient macrophages secrete large amounts of cytokines after stimulation with TLR ligands [16]. In CD4$^+$ T cells, Regnase-1 degrades *Icos*, *Il2*, *Ox40*, and *c-Rel* mRNAs, thereby suppressing aberrant activation of T cells in a cell-intrinsic manner [17].

Therefore, stability of inflammatory mRNAs, of which 3' UTRs carry ARE and/or stem-loop structure, is determined by the balance between degradation and its inhibition by RBPs during TLR or cytokine signaling.

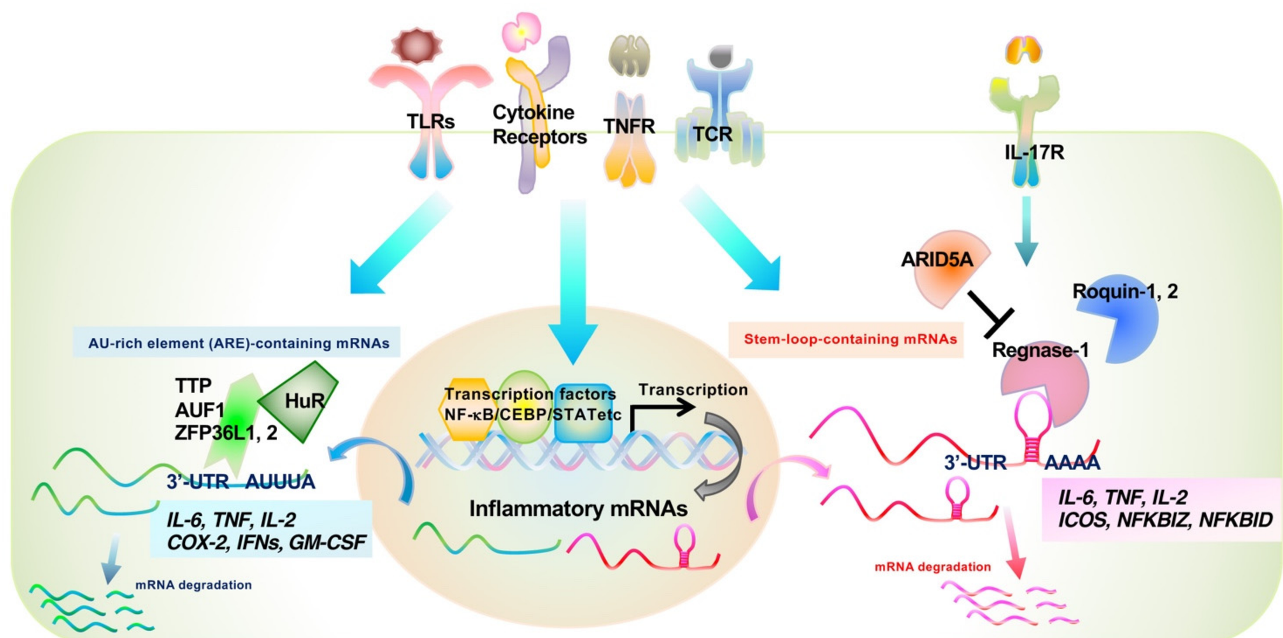

Figure 2. RNA binding proteins are involved in the fate of immune-related mRNAs. Inflammatory mRNAs produced by a variety of immune signaling, harbor multiple cis-elements [9]. AU-rich element (ARE)-containing mRNAs are destabilized by TTP, AUF1 and ZFP36L1, 2, while HuR is responsible for their stabilization. Stem-loop-containing mRNAs are recognized and degraded by Regnase-1 and Roquin-1, 2. ARID5A is proposed to counteract the function of Regnase-1, thereby stabilizing stem-loop-containing mRNAs.

4. Regnase-1 after IL-17 stimulation

Regnase-1 negatively regulates IL-17-induced signals through endoribonuclease activity, resulting in mRNA degradation [18,19]. Some reports have described the regulatory mechanisms of Regnase-1 activity. Upon stimulation with IL-17, TANK-binding kinase 1 (TBK1) and IκB kinase ε (IKKε) are activated through direct interactions with the adaptor protein ACT1 [20–22]. Regnase-1 is then phosphorylated in an ACT1-TBK1/IKKε-dependent manner. Phosphorylated Regnase-1 loses its ability to degrade mRNAs, resulting in the high mRNA expression of IL-17 target genes. In addition, IL-17/ACT1 signaling counteracts constitutively occurring mRNA degradation mediated by Regnase-1. The other possible regulation of Regnase-1 activity is mediated by ARID5A, an RBP. ARID5A binds to the 3′-UTRs of mRNAs and counteracts Regnase-1 in the degradation of mRNAs [19].

Therefore, Regnase-1 activity is strictly regulated through its phosphorylation status, which is controlled by the ACT1-TBK1/IKKε axis, as well as through the counteraction of ARID5A after IL-17-stimulation. Regnase-1 constitutively degrade inflammatory RNAs; however, its functions are inhibited in response to IL-17-stimulation. This post-transcriptional regulation is likely to enable rapid response and turnover of inflammatory mRNAs.

5. IκB-ζ after IL-17-stimulation

Inflammatory cytokines (such as IL-17, IL-1β, and IL-36) promote IκB-ζ mRNA expression through the induction of transcription factors such as NF-κB and signal transducer and activator of transcription (STAT) 3 [23–29]. In this regard, Tyk2, a member of the JAK family, contributes to IκB-ζ gene transcription through the TYK2–STAT3 pathway in keratinocytes [29]. Indeed, the gene encoding IκB-ζ transcript variant 1, which encodes an isoform of IκB-ζ called IκB-ζL, contains a functional STAT3-binding site upstream of the transcription start site. It also contains a binding site for C/EBP near the STAT3-binding site. However, IL-17 is not essential for the induction of IκB-ζ promoter activity because IL-17-induced signaling does not activate STAT3.

IL-17-stimulation stabilizes the transcribed IκB-ζ mRNA in a post-transcriptional manner. The 3′-UTR of IκB-ζ contains a typical sequence and structure that can be recognized by Regnase-1. Regnase-1 constitutively degrades IκB-ζ mRNA to maintain a low expression level. IL-17 promotes Regnase-1 phosphorylation through activation of the ACT1-TBK1/IKKε pathway, leading to loss of function of Regnase-1. Additionally, IL-17 promotes ARID5A expression by recruiting TRAF2, leading to counteraction of IκB-ζ mRNA degradation by Regnase-1. There are some supporting data regarding IκB-ζ mRNA stabilization by IL-17-stimulation [30]. HaCaT cells, a spontaneously transformed keratinocyte cell line, were transfected with siRNA for control (siControl) or TBK1 (siTBK1) and stimulated with IL-17. After IL-17 stimulation, IκB-ζ mRNA was significantly accumulated in siControl-transfected cells but was reduced in transfectants with siTBK1. Notably, IL-17 stimulation failed to promote Regnase-1 phosphorylation in the presence of dimethyl fumarate (DMF), an electrophilic small molecule that alters subcellular localization of ACT1 [30]. Next, HaCaT cells were treated with cycloheximide (CHX), which blocks IκB-ζ mRNA degradation by Regnase-1. Their IκB-ζ mRNA expression level was then monitored. Treatment with CHX

significantly increased IκB-ζ mRNA expression levels. Notably, no additional effects of IL-17-stimulation on the enhancement of IκB-ζ mRNA expression were observed in CHX-treated HaCaT cells. This indicates that the pathway targeted by IL-17 signaling may correspond to Regnase-1 activity.

The IL-17-induced rapid inactivation of Regnase-1 determines IκB-ζ mRNA expression levels. This "releasing-brake" mechanism likely accounts for both preventing IκB-ζ mRNA constitutive overproduction and aiding in a timely rapid accumulation.

6. IκB-ζ in psoriasis

Psoriasis is a chronic inflammatory skin disease characterized by round-to-oval erythematous plaques accompanied by thick adherent scales [31]. The initial inflammatory processes are mainly promoted by Th17 cells, which produce IL-17, IL-21, IL-22, and TNF-α. Subsequent events are dependent on Th1 cells, which produce TNF-α and IFN-γ [32]. These cytokines induce keratinocyte hyperproliferation and production of cytokines, chemokines, and antimicrobial peptides, followed by massive infiltration of immune cells into inflammatory lesions [33–35].

The IκB-ζ protein is a unique member of the inhibitor of nuclear factor κB (IκB) protein family. IκB-ζ mRNA and protein are highly expressed in keratinocytes in psoriatic skin lesions. IκB-ζ plays an essential role in transcriptional induction of various psoriasis-related proteins to promote inflammatory signals, neutrophil chemotaxis, and leukocyte activation. Indeed, systemic or keratinocyte-restricted ablation of the IκB-ζ gene in mice results in diminished systemic inflammation and a low clinical score for psoriasis [26,36]. Similarly, siRNA-mediated local silencing of IκB-ζ in the skin significantly suppresses the clinical symptoms of psoriasis-like skin inflammation [37]. Therefore, IκB-ζ is one of the main players in the onset and development of psoriasis.

7. Possible development of drugs to inhibit IL-17-related signaling

In addition to psoriasis, IL-17 and Th17 cells are involved in T cell-mediated autoimmune diseases such as multiple sclerosis [3,4]. To date, several treatment strategies to inhibit IL-17-related cellular events have been suggested, some of which are now actively approved [4]. Biological agents that can neutralize IL-17 (i.e., secukinumab and ixekizumab) or antagonize its receptor (i.e., brodalumab) are utilized as therapeutic drugs and have high clinical efficacy for the treatment of patients with psoriasis [4]. Jak inhibitors are also believed to confer great therapeutic benefits in controlling the symptoms of autoimmune diseases. However, they sometimes have off-target adverse effects [38]. Since Tyk2-deficient mice grow normally and do not show any abnormal phenotypes under steady-state conditions, a specific inhibitor of Tyk2 may be a suitable target to suppress Th17 functions without severe adverse effects [39–42]. As described above, ACT1, TBK1, and ARID5A promote the loss of Regnase-1 function. This leads to high mRNA expression of immune-related molecules, including IκB-ζ. Thus, peptides, macrocycles, or small-molecule drugs (which inhibit ACT1, TBK1, or ARID5A) may negatively regulate immune responses (including IL-17-signaling)

by enhancing mRNA degradation by Regnase-1. In this regard, fumarate esters, such as DMF, may be suitable drugs for the inhibition of IL-17–induced stabilization of inflammatory mRNAs.

On the other hand, IL-17 also contributes to the pathogenesis of acute respiratory distress syndrome (ARDS) associated with severe SARS-CoV-2 infection [43–45]. Hyperinflammation and lung damage in COVID-19 patients are associated with elevated Th17 cell responses. IL-17 is also elevated in patients with obesity, which may partly explain why obesity is a significant risk factor for developing ARDS associated with COVID-19. A small clinical trial in which patients with COVID-19 were treated with mAbs against IL-17 (netakimab) demonstrated that it decreased lung lesion volume and oxygen support requirement [46]. However, another study showed that treatment with netakimab decreased C-reactive protein levels but failed to decrease the need for mechanical ventilation [47].

8. Conclusions

In this review, we focused on post-transcriptional regulation after IL-17-stimulation. Regnase-1 is the main player in the negative feedback of the signaling pathway. Regnase-1 recognizes stem-loop structures on the 3’ UTR of mRNAs, leading to the degradation of mRNAs encoding inflammatory mediators including IκB-ζ. Although Regnase-1 constitutively reduces the expression levels of inflammatory mRNAs, it is phosphorylated and loses the ability to degrade mRNAs through the ACT1-TBK1/IKKε-axis upon IL-17 stimulation. ARID5A expression, which is induced by IL-17-stimulation, competitively inhibits the binding of Regnase-1 to inflammatory mRNAs. Additional cytokines, including IL-17, play an essential role in the activation of the immune and inflammatory systems to eliminate invading pathogens. However, excess and uncontrolled host defenses can trigger autoimmune diseases. This may explain why inflammatory mRNAs expression is controlled by both transcriptional and post-transcriptional mechanisms.

Th17 cells and IL-17 secretion are central players in the immune and inflammatory systems. Dysregulation is often involved in the onset and development of autoimmune diseases including psoriasis. To date, biological agents that neutralize IL-17 or antagonize its receptor have been utilized as therapeutic drugs and have a high clinical efficacy and tolerability in psoriasis treatment. Recently, low-molecular-weight compounds that inhibit JAK family proteins have been recognized as powerful tools for the treatment of patients with autoimmune and chronic inflammatory diseases. As described here, several inflammatory mRNAs are negatively regulated through their degradation by Regnase-1. After stimulation with inflammatory cytokines, including IL-17, Regnase-1 is phosphorylated and loses its degradation capacity. This leads to the high expression of inflammatory mRNAs, such as IκB-ζ. Thus, inhibition of negative regulators of Regnase-1, such as the ACT1-TBK1/IKKε pathway and ARID5A, is likely to be a novel and convenient systemic therapeutic strategy with high efficacy. DMF, which electrophilically inhibit ACT1, has potential applications. We hope that novel materials that can modify post-transcription regulation will be successfully developed to improve the clinical symptoms and severity of patients with immune and chronic inflammatory diseases.

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Conflict of interest

All authors declare no conflicts of interest in this paper.

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